#### (19) World Intellectual Property Organization International Bureau



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#### (43) International Publication Date 20 June 2002 (20.06.2002)

#### (10) International Publication Number WO 02/048165 A3

- (51) International Patent Classification7: C07H 19/00, 19/207, C07D 307/88, C07F 9/655, A61K 31/70, 31/343, 31/665, A61P 35/00
- (21) International Application Number: PCT/US01/49231
- (22) International Filing Date:

17 December 2001 (17.12.2001)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/256,066

15 December 2000 (15.12.2000)

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- (81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZM, ZW.
- (84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

#### Published:

- with international search report
- (88) Date of publication of the international search report:

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: ANTIVIRAL AGENTS FOR TREATMENT OF FLAVIVIRIDAE INFECTIONS

(57) Abstract: The disclosed invention is a composition for and a method of treating Flaviviridae (Hepacivirus, Flavivirus, Pestivirus) infections, including BVDV and HCV, and abnormal cellular proliferation in a host, including animals, and especially humans, using a small molecule or its pharmceutically acceptable salt or prodrug.

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A. CLASSIFICATION OF SUBJECT MATTER
1PC 7 C07H19/00 C07H19/207 A61K31/70 C07F9/655 C07D307/88 A61P35/00 A61K31/343 A61K31/665 According to International Patent Classification (IPC) or to both national classification and IPC B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) CO7H CO7D CO7F A61K A61P IPC 7 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the International search (name of data base and, where practical, search terms used) EPO-Internal, WPI Data, PAJ, CHEM ABS Data C. DOCUMENTS CONSIDERED TO BE RELEVANT Citation of document, with indication, where appropriate, of the relevant passages Relevant to claim No. Category ° 1,2,8,9, 15,16, X WO 94 29331 A (SLOAN KETTERING INST CANCER ;UNIV ROCHESTER (US)) 36,37, 22 December 1994 (1994-12-22) 43,44, 50,51, 60-63,68 claims 1-3,8,11,22 -/--Further documents are listed in the continuation of box C. Patent family members are listed in annex. Х Special categories of cited documents : "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the "A" document defining the general state of the art which is not considered to be of particular relevance earlier document but published on or after the international filling date "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. "O" document referring to an oral disclosure, use, exhibition or other means document published prior to the international filing date but later than the priority date claimed "&" document member of the same patent family Date of mailing of the international search report Date of the actual completion of the international search 23. 07. 2002 24 April 2002 Authorized officer Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016 Fitz, W

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CIC	odica) DOCUMENTO CONCRETA CONTRACTOR DE CONT	PC1/05 01/49231		
Category °	DOCUMENTS CONSIDERED TO BE RELEVANT  Citation of document, with Indication, where appropriate, of the relevant passages			
	Chauth of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.		
Х	WO 98 15563 A (CODON PHARMACEUTICALS INC) 16 April 1998 (1998-04-16)  page 98, line 19; page 99, lines 1,19;	1,2,8,9, 15,16, 36,37, 43,44, 50,51, 60-63,68		
;	page 100, lines 26,29,32; page 101, line 3; page 105, line 17; page 106, lines 1,17; page 107, lines 10-21; page 23, lines 19-29; page 3, lines 5-19			
X	US 5 658 890 A (PANKIEWICZ KRYSZTOF W ET AL) 19 August 1997 (1997-08-19)	1,2,8,9, 15,16, 36,37, 43,44, 50,51, 60-63,68		
	examples 1,2,7,8; column 2, lines 29-64			
X	LESIAK K ET AL: "SYNTHESIS OF NONHYDROLYZABLE ANALOGUES OF THIAZOLE-4-CABOXAMIDE ANDBENZAMIDE ADENINE DINUCLEOTIDE CONTAINING FLUORINE ATOM AT THE C2' OF ADENINE NUCLEOSIDE: INDUCTION OF K562 DIFFERENTIATION AND INOSINE MONOPHOSPHATE DEHYDROGENASE INHIBITORY ACTIVITY"  JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 40, 1997, pages 2533-2538, XP002920574 ISSN: 0022-2623 page 2534, compounds 10-12; page 2533, columns 1 and 2	1,2,8,9, 15,16, 36,37, 43,44, 50,51, 60-63,68		
(	WO 98 34942 A (INSPIRE PHARMACEUTICALS INC; RIDEOUT JANET L (US); PENDERGAST WILL) 13 August 1998 (1998-08-13) page 4, Table 1, Ac2C-NAD, Ac2C-PAD, Ap2BAD; page 7, lines 5-14	1,8,15		
	RILEY T A: "SYNTHESIS OF 2(BETA-D.RIBOFURANOSYL) PYRIMIDINES, A NEW CLASS OF C-NUCLEOSIDES" JOURNAL OF HETEROCYCLIC CHEMISTRY, HETEROCORPORATION. PROVO, US, vol. 24, 1 July 1987 (1987-07-01), pages 955-964, XP000575823 ISSN: 0022-152X page 958, compound 20	1		
	<b>-/-</b> -			

International Application No
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C (Continue	ntion) DOCUMENTS CONSIDERED TO BE RELEVANT	PC1/05 01/49231		
Category °	Citation of document, with indication, where appropriate, of the relevant passages		Relevant to claim No.	
A	US 4 748 173 A (NELSON PETER H ET AL) 31 May 1988 (1988-05-31)	1,8,15, 22,29, 36,43, 51-55, 60-63		
	abstract; claim 1		00-05	
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International application No. PCT/US 01/49231

# INTERNATIONAL SEARCH REPORT

Box I	Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)
This Inte	emational Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:
1. X	Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
	Although claims 22-53,56-68 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.	Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
з. 🗌	Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).
Box []	Observations where unity of invention is lacking (Continuation of item 2 of first sheet)
This Inte	mational Searching Authority found multiple inventions in this international application, as follows:
	see additional sheet
1.	As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.	As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.	As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. X	No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  1,2,8,9,15,16,22,23,29,30,36,37,43,44,50-55,60-63,68 partially
Remark	on Protest  The additional search fees were accompanied by the applicant's protest.  No protest accompanied the payment of additional search fees.

### FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1,2,8,9,15,16,22,23,29,30,36,37,43,44,50-55,60-63, 68 partially

Dinucleoside diphosphate derivatives of formula I, claim 1, wherein R is a nucleoside analogue with a 6-membered heterocycle as defined in formulae II and III; pharmaceutical compositions containing them; uses thereof.

2. Claims: 1,2,8,9,15,16,22,23,29,30,36,37,43,44,50-55,60-63, 68 partially

Nucleoside diphosphate derivatives of formula I, claim 1, wherein R is a mycophenol derivative with a sidechain of at least 3 C-atoms as defined in formula IV; pharmaceutical compositions containing them; uses thereof.

3. Claims: 3,10,17,24,31,38,45,56-59, 64-67 completely; claims 1,2,8,9,15,16,22,23,29,30, 36,37,43,44,50-55,60-63,68 partially

Nucleoside diphosphate derivatives of formula I, claim 1, wherein R is a mycophenol derivative with a C2-sidechain as defined in formula V; pharmaceutical compositions containing them; uses thereof.

4. Claims: 2,9,16,23,30,37,44,50-55,60-63,68 partially

Thiazofurin derivatives as defined in claim 2; pharmaceutical compositions containing them; uses thereof.

5. Claims: 4,11,18,25,32,39,46,50-55,60-63,68 partially

Derivatives of mycophenolic alcohols, aldehydes and acids with a C2-sidechain as defined in claim 4; pharmaceutical compositions containing them; uses thereof.

6. Claims: 4,11,18,25,32,39,46,50-55,60-63,68 partially

Derivatives of mycophenolic alcohols, aldehydes and acids with a C4-sidechain as defined in claim 4; pharmaceutical compositions containing them; uses thereof.

7. Claims: 4.11,18,25,32,39,46,50-55,60-63,68 partially

## FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Derivatives of mycophenolic alcohols, aldehydes and acids with a C6-sidechain as defined in claim 4; pharmaceutical compositions containing them; uses thereof.

8. Claims: 5,12,19,26,33,40,47,50-55,60-63,68 partially

Mycophenolic phosphates, phosphonates and sulfonates with a C2-sidechain as defined in claim 5; pharmaceutical compositions containing them; uses thereof.

9. Claims: 5,12,19,26,33,40,47,50-55,60-63,68 partially

Mycophenolic phosphates, phosphonates and sulfonates with a C2-sidechain as defined in claim 5; pharmaceutical compositions containing them; uses thereof.

10. Claims: 6,13,20,27,34,41,48 completely; claims 50-55, 60-63,68 partially

Mycophenolic hydrocarbyl derivatives as defined in claim 6; pharmaceutical compositions containing them; uses thereof.

11. Claims: 7,14,21,28,35,42,49-55,60-63,68 partially

Derivatives of mycophenolic diphosphates with a C2-sidechain as defined in claim 7; pharmaceutical compositions containing them; uses thereof.

12. Claims: 7,14,21,28,35,42,49-55,60-63,68 partially

Derivatives of mycophenolic diphosphates with a C4-sidechain as defined in claim 7; pharmaceutical compositions containing them; uses thereof.

International Application No
PCT/US 01/49231

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 9429331	A	22-12-1994	US AU WO US US	5569650 A 7171794 A 9429331 A1 5658890 A 5700786 A	29-10-1996 03-01-1995 22-12-1994 19-08-1997 23-12-1997
WO 9815563	A	16-04-1998	AU BR CN EP JP WO US	4815197 A 9712285 A 1239964 A 0934325 A1 2001501952 T 9815563 A1 6326490 B1	05-05-1998 20-11-2001 29-12-1999 11-08-1999 13-02-2001 16-04-1998 04-12-2001
US 5658890	A	19-08-1997	US AU WO US	5569650 A 7171794 A 9429331 A1 5700786 A	29-10-1996 03-01-1995 22-12-1994 23-12-1997
WO 9834942	A	13-08-1998	US AUUURR CCEPPPOOZZOS WOOSAS Z	5900407 A 5837861 A 735684 B2 6324198 A 738907 B2 6324298 A 9807169 A 9809562 A 1292795 T 1250369 T 1003474 A1 0981534 A2 2001504858 T 2001526635 T 993776 A 993777 A 337225 A 337405 A 9834593 A1 9834593 A1 9834593 A1 9834593 A1 9834593 A1 9800979 A 2001031743 A1 9801073 A	04-05-1999 17-11-1998 12-07-2001 26-08-1998 27-09-2001 26-08-1998 06-06-2000 02-10-2001 12-04-2001 12-04-2000 31-05-2000 01-03-2000 10-04-2001 18-12-2001 18-12-2001 27-07-2001 13-08-1999 28-03-2002 27-07-2001 13-08-1998 13-08-1998 19-02-1999 18-10-2001 19-02-1999
US 4748173	Α	31-05-1988	US US US	4727069 A 4861776 A 5177072 A	23-02-1988 29-08-1989 05-01-1993